The Annals of Thoracic Surgery

Combined degenerative mitral valve and coronary surgery: early outcomes and 10-year survival

--Manuscript Draft--

Manuscript Number:	ANNALS-19-02058R2
Article Type:	Original Article
Section/Category:	Adult Cardiac
Keywords:	mitral regurgitation, degenerative mitral valve surgery, coronary surgery, survival.
Manuscript Classifications:	Coronary artery bypass grafts, CABG; Mitral valve; Mitral valve repair; Outcomes
Corresponding Author:	Raimondo Ascione, M.D., ChM, FRCS Bristol Heart Institute, University of Bristol Bristol, United Kingdom
First Author:	Vito Domenico Bruno
Order of Authors:	Vito Domenico Bruno
	Mustafa Zakkar
	Gustavo Guida
	Filippo Rapetto
	Asif Rathore
	Raimondo Ascione, M.D., ChM, FRCS
Manuscript Region of Origin:	UNITED KINGDOM
Abstract:	Background: To investigate the impact of combined degenerative mitral valve (DMV) and coronary artery bypass grafting surgery (CABG+DMV) versus DMV surgery only on in-hospital health outcome and 10-year survival. Methods: 745 patients with DMV disease were identified. Of these, 186 (24.9%) were affected also by coronary disease receiving combined DMV+CABG. They were compared with the remaining 559 patients receiving DMV only surgery in terms of in-hospital, 1, 5, and 10-year survival. We evaluated a short-term composite outcome of hospital mortality, acute kidney injury, cerebro-vascular events and low cardiac output requiring postoperative use of intra-aortic balloon pump. In addition, we assessed mitral valve repair rates over time and their correlation with long-term survival. To minimise bias, we conducted a propensity score matching. Results: DMV+CABG surgery was associated with a similar incidence of composite endpoint compared to DMV surgery alone (6.5 vs 5.4 %, p=0.71 in the unmatched analysis and 7.5% vs 8.2%, p=0.82 in the matched analysis). 10-year survival was 70.5 vs 68.6 % (p=0.07) for the unmatched analysis and 64.6 vs 62.5 % (p=0.9) for the matched analysis, DMV+CABG vs DMV only respectively. Mitral valve repair had a beneficial effect on short term outcomes and long-term mortality rates, regardless the presence of concomitant coronary surgery. Conclusions : Combined DMV+CABG surgery is a very effective surgical treatment with high mitral valve repair rate. Early in-hospital outcome and long-term survival are comparable with DMV only surgery. In these combined procedures mitral valve repair is associated with better long-term survival.

Combined degenerative mitral valve and coronary surgery: early outcomes and 10-year survival

Short title: Degenerative mitral and coronary surgery

Vito D. Bruno[1], PhD Mustafa Zakkar[1], PhD Gustavo Guida[1], MD Filippo Rapetto[1], MD Asif Rathore[1], FRCS and Raimondo Ascione[1], FRCS

[1]Bristol Heart Institute, School of Clinical Sciences, University of Bristol, Bristol, UK

Corresponding author: Professor Raimondo Ascione
Chair of Cardiac Surgery & Translational Research
Faculty of Health Science
University of Bristol
Marlborough Street,
BS2 8HW, Bristol, UK
Email: r.ascione@bristol.ac.uk

Total Word count: 4667

Key words: mitral regurgitation, degenerative mitral valve surgery, coronary surgery, survival.

Abstract

Background: To investigate the impact of combined degenerative mitral valve (DMV) and coronary artery bypass grafting surgery (CABG+DMV) versus DMV surgery only on in-hospital health outcome and 10-year survival.

Methods: 745 patients with DMV disease were identified. Of these, 186 (24.9%) were affected also by coronary disease receiving combined DMV+CABG. They were compared with the remaining 559 patients receiving DMV only surgery in terms of in-hospital, 1, 5, and 10-year survival. We evaluated a short-term composite outcome of hospital mortality, acute kidney injury, cerebro-vascular events and low cardiac output requiring postoperative use of intra-aortic balloon pump. In addition, we assessed mitral valve repair rates over time and their correlation with long-term survival. To minimise bias, we conducted a propensity score matching.

Results: DMV+CABG surgery was associated with a similar incidence of composite endpoint compared to DMV surgery alone (6.5 vs 5.4 %, p=0.71 in the unmatched analysis and 7.5% vs 8.2%, p=0.82 in the matched analysis). 10-year survival was 70.5 vs 68.6 % (p=0.07) for the unmatched analysis and 64.6 vs 62.5 % (p=0.9) for the matched analysis, DMV+CABG vs DMV only respectively. Mitral valve repair had a beneficial effect on short term outcomes and long-term mortality rates, regardless the presence of concomitant coronary surgery.

Conclusions*:* Combined DMV+CABG surgery is a very effective surgical treatment with high mitral valve repair rate. Early in-hospital outcome and long-term survival are comparable with DMV only surgery. In these combined procedures mitral valve repair is associated with better long-term survival.

Abstract word count: 250

List of abbreviations

AKI: Acute Kidney Injury

CABG: Coronary artery bypass grafting

CCS: Canadian Cardiovascular Society

CPB: Cardio-Pulmonary Bypass

CT: Computed Tomography

CVA: Cerebro Vascular Accidents

DMV: Degenerative Mitral Valve

DMV+ CABG: Degenerative mitral valve associated to coronary artery bypass grafting

HR: Hazard Ratio

IABP: Intra-Aortic Balloon Pump

IMV: Ischaemic Mitral Valve

IQR: Inter-quartile Range

LCO: Low Cardiac Output

LVEF: Left Ventricular Ejection Fraction

MI: Myocardial Infarction

MR: Mitral Regurgitation

MV: Mitral Valve

NHS: National Health Service

NYHA: New York Heart Association

OR: Odds Ratio

PCI: Percutaneous Coronary Intervention

SMD: Standardised Mean Difference

UK: United Kingdom

US: United States

Combined coronary artery bypass grafting (CABG) and valve surgery is generally considered a predictor of mortality, complications and reduced long-term survival [1]. Data from the UK and USA registries suggest that combined mitral valve (MV) and coronary surgery is associated with a 3 to 5 folds increase of post-operative mortality compared to isolated MV procedures [1,2]. The UK registry suggests that in 2015 the 30-day mortality rate for combined MV and coronary surgery was 5.16% versus 2.83% for isolated MV surgery [2] and a recent report from >1200 US MEDICARE Hospitals suggests that combined MV and CABG surgery is associated with hospital mortality of >10% and reduced long-term survival rates [1]. However, this report generalises across the whole MV surgery spectrum, with no distinction across the different types of MV disease. Patients with ischemic mitral valve (IMV) disease undergoing combined IMV+CABG surgery are genuinely at high risk of in-hospital mortality and reduced long-term survival [3]. Conversely, surgery for isolated degenerative mitral valve (DMV) disease is associated with lower mortality rate and superior long-term survival rates, especially when reparative techniques are used in high-volume centres [1,4,5]. Only few studies have investigated the impact of combined DMV and CABG surgery (DMV+CABG) on health outcomes [6]. Hence, outcome data associated with combined DMV+CABG are either still missing or poorly understood. Key examples of missing data include actual rates of in-hospital mortality and complications, long-term survival, reliability of logistic Euroscore in predicting mortality and impact of combined DMV+CABG on MV repair rates [7]. The aim of this study was to investigate the impact of the specific combination of degenerative mitral valve plus coronary (DMV+CABG) surgery versus DMV alone on 30-day mortality, hospital complication rates, MV repair rates, and on 1, 5, and 10-year survival and reoperation rates. In addition, we evaluated the impact of the MV repair on the risk of early and long-term mortality in combined procedures compared to isolated DMV.

Patients and Methods

The key rationale for designing this study was to test the null hypothesis that CABG would not increase operative risks when specifically combined with degenerative MV disease. To this end we elected to undertake a retrospective analysis of prospectively collected data derived from our internal database validated and stored by an independent team, as part of the UK National Registry for Cardiac Surgery. The study protocol followed the local Institutional Clinical Audit Review Board and patient consent was waived.

Patient selection

Patient selection is shown in **Figure 1**. From January 2000 to March 2015 a total of 1,742 patients underwent any procedures involving mitral valve surgery at our institution (for more details see **Supplemental table 1 and 2 and Supplemental file** Patient Selection). A propensity matched analysis was conducted to minimize the impact of preoperative differences: after matching, 134 patients for each group were compared.

Data collection and clinical management

Baseline data included clinical characteristics, symptom status and past medical history of the patients. Logistic Euroscore was calculated according to established method [8]. Diagnosis of severe DMV and coronary disease was based on clinical history, preoperative echocardiograms and baseline coronary angiography. Elective patients were defined as those admitted from home, whereas urgent patients were those admitted from another hospital and requiring surgery within 7-10 day before discharge. Left ventricular ejection fraction (LVEF) was derived from baseline echocardiogram and classified as reduced if less than 50%. The surgical technique and postoperative care used was in keeping with surgeon's preference (for more details see **Supplemental file** – Surgical Technique and Outcomes). Intraoperative and postoperative data collection and clinical management was as previously reported [9,10]. Late survival data after discharge were obtained from the UK National Health Service (NHS) tracing service with the latest data obtained in June 2015.

Outcome Measures and definitions

We used a composite outcome of in-hospital mortality, acute kidney injury (AKI), cerebro-vascular accidents (CVA) and severe low cardiac output (LCO). We also collected generic in-hospital outcome including reopening for bleeding, duration of hospital stays,1, 5 and 10-year survival as well as 5- and 10-years MV reoperation rates. In-hospital mortality was defined as a death by any cause occurred at any time before discharge regardless the length of hospital stays. CVA consisted of any new post-operative stroke identified clinically and/or by Computed Tomography (CT) scan. Occurrence of acute kidney injury was defined as need for postoperative hemofiltration/dialysis. Severe LCO was defined as the need to insert intra-operatively or postoperatively an intra-aortic balloon pump (IABP). Overtime, the rate of MV repair in both groups was assessed across consecutive 5-yer time periods.

Statistical analysis

Data are presented as mean ± one standard deviation for numerical variables that were normally distributed and as median and interquartile range (IQR) for the numerical variables not normally distributed. Categorical variables are shown as count and percentages. Comparison between numerical variables has been conducted using unpaired Student t-test if normally distributed and Mann-Whitney U test if not normally distributed. Categorical variables have been compared using Pearson Chi-square test or Fisher exact test as appropriate. A multiple logistic regression model has been used to identify predictors of in-hospital mortality: the final model was obtained with a stepwise approach. Survival analysis was conducted comparing the survival functions of the two groups using Log-Rank test and Kaplan Meier Curves. In addition, a propensity score matching analysis was conducted to account for differences in baseline characteristics between groups. The matching process included the following variables: gender, New York Heart Association (NYHA) class, Canadian Cardiovascular Society (CCS) class, diabetes, hypertension, smoking history, peripheral vascular disease, logistic Euroscore, use of baseline inotropes, previous percutaneous coronary intervention (PCI), previous myocardial infarction (MI), reduced LVEF (<50%), nonelective surgery and re-operation. The nearest neighbour method was used, and the balance checked with standardised mean differences (SMD). After propensity score matching, variables were compared using paired Student t-test or paired Wilcoxon test for continuous variables and McNemar (for dichotomous variables) and Chi-square test for ordinal categorical variables and a conditional logistic regression model accounting for matching index was developed to evaluate the predictors of the in-hospital mortality. Patients were also divided by time-period of observation to allow a descriptive sub-analysis of changes in MV repair rate and key early health outcome overtime. All tests were two-sided with the alpha level set at 0.05 for statistical significance. Missing values were addressed with simple imputation methods. The statistical analysis was computed using R version 3.0.2 (R Core Team. R Foundation for Statistical Computing, Vienna, Austria).

Results

Preoperative characteristics of the patients before and after propensity score matching are shown in **Table 1.**

Unmatched analysis

The mean age of the overall population was 67.6 ± 11.8 years and logistic Euroscore was significantly higher in the DMV+CABG group (median 6 (IQR= 5-8) vs 5 (IQR = 3-7), $p < 0.01$).

Intra-operative characteristics and post-operative outcomes of unmatched analysis are shown in **Table 2**. As expected, cardiopulmonary bypass (CPB) time and aortic cross clamp times were longer in the DMV+CABG group. The predefined composite outcome did not differ between groups (6.5 % vs 5.4%, p=0.71). In-hospital mortality rate was 5.9% vs 3.8% (p = 0.29); CVA was 0% vs 1.3 % (p=0.27); AKI was 1.6% vs 0.9% (p = 0.68), while the occurrence of LCO was 0.0% in both groups, all DMV+CABG group vs DMV only group respectively. Reopening for bleeding was 6.9% vs 4.5% (p=0.71). Length of hospital stay was longer in this DMV+CABG vs DMV only group (median 9.5 vs 8 days (p = 0.04). The univariable logistic regression model did not identify DMV+CABG as an independent predictor of the composite (OR 1.61, 95% CI 0.73-3.34, p = 0.21) or of in-hospital mortality (OR 1.61, 95% CI 0.73-3.34, p = 0.21). The adjusted multiple logistic regression model confirmed that DMV+CABG is neither a predictor of the predefined composite endpoint nor of in-hospital mortality. This model identified 3 predictors of in-hospital mortality including the use of MV replacement (OR 2.52, 95% CI 1.14-5.73, p =0.02), logistic Euroscore (OR 1.40, 95% CI 1.23 – 1.50, p < 0.01), and prolonged CPB time (OR 1.01, 95% CI 1.002-1.02, p = 0.01). Long term survival rates for the unmatched analysis were similar between the two groups (**Figure 2-A**): DMV+ CABG patients had a survival rate of 94.4% at 1 year, 77.5% at 5-year and 63% at 10 years vs 93.2% at 1 year, 85.3% at 5 years and 70.6% at 10 years for the DMV only group (p = 0.18). DMV+CABG did not affect the survival rates when assessed by a Cox proportional Hazard model (HR 1.58, 95% CI 0.87-2.04, p = 0.18).

Matched analysis

After propensity score matching (**Table 1**) the surgical operative times were found to be longer in the DMV+CABG with a median CPB time of 127 minutes vs 114 minutes in the DMV only group (p = 0.02) and a median aortic cross-clamp time of 85 vs 80 minutes respectively (p = 0.16). The MV repair rates were 59.7% vs 68.9%, p=0.2. in the DMV+CABG vs DMV alone groups respectively. The predefined composite outcome did not differ between groups (7.5 % vs 8.2%, p=0.82). In-hospital mortality was 6.7% in the DMV+CABG vs 4.5% for the DMV only group (p=0.44), while post-operative CVA was 0% vs 2.2 (p = 0.65), post-operative dialysis was 1.5 vs 2.2% (p = 0.65), and LCO was 0.0% in both groups, respectively. Length of hospital stay was also similar between the groups: median 9 (IQR 7-12.8) vs median 9(IQR 7-13.8) respectively (p = 0.35). The survival rates were 88 % at 1 year, 74.5 % at 5 years and 64.6% at 10 years for the DMV+CABG group and 89.2% at 1 year, 73.9% at 5 years and 62.5% at 10 years for the DMV only group(p=0.9) (**Figure 2-B**). No independent predictors of mortality were found.

Rates of mitral valve repair overtime and impact on short- and long-term outcome

The overall MV repair rates were 62.9% vs 70.7%, (p=0.06) in the DMV+CABG vs DMV alone groups respectively. Differences in MV repair and health outcome by time-period are shown in **Table 3 and Figure 3**. The period between year 2000 and 2004 was characterised by a low rate of MV repair in our centre. However, this increased significantly after year 2004 with a peak of MV repair rate of 88.5% in 2009 (**Figure 3**). The main health outcomes at different time periods is shown in **Table 3**: mortality rate was lower in the period between 2005-2009, while the lowest rate of composite health outcome was found in the final part of the series in concomitance with the highest repair rate. Higher rates of MV repair were also associated with higher long-term survival with an HR of 0.46 (95% CI 0.35-0.66). When adjusted for combined procedure (CABG) and cross-clamp time the beneficial effect of the MV repair on long-term survival was still confirmed (HR 0.47, 95% CI 0.33-0.68), showing that the complexity and the length of the surgery has no impact on the intrinsic beneficial effect of the repair procedure. During the follow up time, fifteen patients (2.01%) underwent a reoperation. Of these, 12 procedures (1.63%) consisted of re-operations involving the mitral valve including 10 isolated MV reoperations and 2 procedures combined with aortic valve replacement. Of note, freedom from MV reoperation at 10 years was 97.2% for the DMV+CABG group and 97.9% for the DMV only group(p=0.61).

Comment

The combination of CABG and valve procedures has been generally associated with worst outcome after cardiac surgery [1,11-13]. Combined MV and CABG surgery has been largely investigated in the context of ischaemic mitral valve disease [14,15] with the results of this MV specific disease often uncritically generalised across the non-ischemic mitral disease spectrum[1], affecting the informed consenting of patients and the decision-making process toward percutaneous and/or medical treatment alternatives [16-18]. Yet, little is known on the outcome of DMV+CABG surgery [6,19].

Our study shows that combined DMV+CABG has a similar rate of mortality, hospital complications, MV repairs, and long-term survival compared to DMV surgery alone. These findings highlight that patients afflicted by combined severe DMV and coronary disease should be offered combined DMV+CABG surgery instead of alternative and less validated alternatives.

In this study, DMV+CABG surgery was not associated with worse outcome compared with DMV surgery alone for any of the health outcome measured. The only consistent difference observed was the longer CPB time in the combined group. Even in the unmatched analysis all the outcome measures evaluated showed similar results compared to DMV only group. A recent large report from US [1] found CABG to be an independent predictor of both short and long-term mortality, while this was not the case in our study. However, the study population of the US report [1] was on average 5 years older compared to our patient cohort and encompassed a variety of valve pathologies and surgical procedures. Hence, a comparative evaluation is not appropriate as the observed results could reflect differences in baseline risk profile, surgical and anaesthetic practice as well as a different period of observation. In addition, observed outcome in the two studies might also reflect differences in volume of MV surgery and MV repair rates between centres [1]. In this study the rates of MV repair was 68.7% with no differences between groups, despite is an historical series, with 25% of patients receiving non-isolated MV, 8.2% having redo surgery, median age being 70 years, and 25% of patients being urgent admissions. As expected, the rate of MV repair rose over time reaching 85-90% by 2008. Of note, MV repair was associated with better short-term outcome and long-term survival.

Previous studies have suggested that Euroscore may underestimate the mortality risk for combined surgery: in a study published in 2004, Karthik and colleagues reported a mortality rate after CABG plus valve surgery of 8.7% compared to a predicted value (additive Euroscore) of 6.7% [20]. Similar results were reported in another study suggesting that the Euroscore underestimated the impact of combined procedures (O/E = 1.09, $p < 0.001$) [21].

The findings of this study confirm that combined DMV+CABG surgery is associated with low in-hospital risk and excellent long-term survival particularly when MV repair is used. This confirms that a surgical practice by MV repair expertise may improve patient benefit and use of hospital resources. In addition, these findings may help the decision-making process toward surgery, instead of less validated percutaneous techniques or medical treatment alone. Recent evidence from meta-analysis and randomised trial suggest that the mitral clip procedure is associated with a very high rate of on table residual 2+ mitral regurgitation (MR), 7.3% of mortality at 1 year, and a freedom from combined death, repeat surgery, or grade 3+ or 4+ recurrent MR of only 39.8% at 4 years. These reports also highlight a need for open reoperation rates at 4 year of 25% in patients undergoing primary mitral clip treatment [22,23]. This study also suggests that patients needing combined DMV+CABG should not be regarded at high risk. Instead they should be referred for conventional surgery to high-volume MV repair surgery centres for consideration.

The logistic regression model analysis did not identify DMV+CABG surgery as an independent predictor of mortality, while it confirmed that replacing the MV instead of repairing it is associated with worse health outcome. Others have already underlined this concept by showing that MV repair is the preferred option in these patients [7] with a reduced incidence of complications and mortality rate [24].

There are limitations to this study: it is a retrospective analysis and no data is presented on long-term cardiac related events including recurrence of MR and quality of life/symptoms. In addition, a relatively small number of patients was under observation at 10-year follow-up. However, our series with 100% follow-up survival data, low rate of early composite endpoint and very good long-term survival is still a valuable and real reflection of clinical efficacy and patient well-being. In addition, very few patients in the DMV only group (n=24) had mild or moderate coronary disease for which the Heart Team did not indicate the need for combined CABG surgery. Another possible limitation is related to the risk of Type II error and therefore the risk of non-rejection of a false null hypothesis as concomitant CABG is a recognised risk factor in valve surgery, hence larger studies are required to confirm our findings.

In conclusion this study suggests that combined DMV+CABG surgery is safe and effective with a 30-day mortality, complication rates, MV repair rates, and 1, 5, and 10-year survival comparable to DMV surgery only. It also indicates that MV repair should be the first choice in these combined cases of degenerative mitral valve and coronary disease due superior short-term health outcome and long-term survival beneficial effects. These findings, if confirmed by larger studies, have important clinical implications in terms of both referral pathways by surgical MV repair expertise and patient informing/consenting.

References

1. Vassileva CM, McNeely C, Spertus J, Markwell S, Hazelrigg S. Hospital volume, mitral repair rates, and mortality in mitral valve surgery in the elderly: An analysis of US hospitals treating Medicare fee-for-service patients. J Thorac Cardiovasc Surg. 2015;149(3):762-768.e1.

2. Bridgewater B, Keogh B, Kinsman R, Walton P. SCTS 6th National Adult Cardiac Surgical Database Report 2008.; 2008.

3. Wang L, Li B, Liu C, Rong T, Yu Y, Gu C. Short- and Medium-Term Effects of Combined Mitral Valve Surgery and Coronary Artery Bypass Grafting Versus Coronary Artery Bypass Grafting Alone for Patients with Moderate Ischemic Mitral Regurgitation: A Meta-Analysis. J Cardiothorac Vasc Anesth. 2016;30(6):1578-1586.

4. Coutinho GF, Antunes MJ. Mitral valve repair for degenerative mitral valve disease: surgical approach, patient selection and long-term outcomes. Heart. 2017;103(21):1663-1669.

5. Bridgewater B, Hooper T, Munsch C et al. Mitral repair best practice: proposed standards. Heart. 2006;92(7):939-944.

6. Dahlberg PS, Orszulak TA, Mullany CJ, Daly RC, Enriquez-Sarano M, Schaff H V. Late outcome of mitral valve surgery for patients with coronary artery disease. Ann Thorac Surg. 2003;76(5):1539-1548.

7. Javadikasgari H, Gillinov AM, Idrees JJ et al. Valve Repair Is Superior to Replacement in Most Patients With Coexisting Degenerative Mitral Valve and Coronary Artery Diseases. Ann Thorac Surg. 2016. 103(6):1833-1841.

8. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J. 2003;24(9):881-882.

9. Zakkar M, Bruno VD, Guida G, et al. Postoperative acute kidney injury defined by RIFLE criteria predicts early health outcome and long-term survival in patients undergoing redo coronary artery bypass graft surgery. J Thorac Cardiovasc Surg. 2016:152(1): 235-42.

10. Bruno VD, Zakkar M, Rapetto F et al. Early health outcome and 10-year survival in patients undergoing redo coronary surgery with or without cardiopulmonary bypass: a propensity score-matched analysis. Eur J Cardiothorac Surg. 2017;52(2):945-951.

11. Nicolini F, Agostinelli A, Fortuna D et al. Outcomes of patients undergoing concomitant mitral and aortic valve surgery: results from an Italian regional cardiac surgery registry. Interact Cardiovasc Thorac Surg. 2014;19(5):763-770.

12. Hannan EL, Racz MJ, Jones RH et al. Predictors of mortality for patients undergoing cardiac valve replacements in New York State. Ann Thorac Surg. 2000;70(4):1212-1218.

13. Leavitt BJ, Baribeau YR, DiScipio AW et al. Outcomes of patients undergoing concomitant aortic and mitral valve surgery in northern New England. Circulation. 2009;120(11 Suppl). S155-62.

14. Buja P, Tarantini G, Del Bianco F et al. Moderate-to-severe ischemic mitral regurgitation and multivessel coronary artery disease: Impact of different treatment on survival and rehospitalization. Int J Cardiol. 2006;111(1):26-33.

15. Fattouch K, Guccione F, Sampognaro R et al. POINT: Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. J Thorac Cardiovasc Surg. 2009;138(2):278-285.

16. Roques F, Nashef SA, Michel P et al. Risk factors and outcome in European cardiac surgery : analysis of the EuroSCORE multinational database of 19030 patients Risk factors and outcome in European cardiac surgery : analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15(6):816-822.

17. Shahian DM, He X, Jacobs J et al. The STS AVR+CABG Composite Score : A Report of the STS Quality Measurement Task Force. Ann Thorac Surg. 2014;97(5):1604-1609.

18. Hannan EL, Racz M, Culliford AT et al. Risk Score for Predicting In-Hospital / 30-Day Mortality for Patients Undergoing Valve and Valve/Coronary Artery Bypass Graft Surgery. Ann Thorac Surg. 2013;95(4):1282-1290.

19. Davarpasand T, Hosseinsabet A, Jalali A. Concomitant coronary artery bypass graft and aortic and mitral valve replacement for rheumatic heart disease : short-and mid-term outcomes. Interact Cardiovasc Thorac Surg 2015;21(May):322-328.

20. Karthik S, Srinivasan AK, Grayson AD et al. Limitations of additive EuroSCORE for measuring risk stratified mortality in combined coronary and valve surgery. Eur J Cardiothorac Surg 2004;26(2):318-322.

21. Atik FA, Cunha CR. Impact of type of procedure and surgeon on EuroSCORE operative risk validation. Rev Bras Cir Cardiovasc 2014;29(2):131-139.

22. Wan B, Rahnavardi M, Tian DH et al. A meta-analysis of MitraClip system versus surgery for treatment of severe mitral regurgitation. Ann Cardiothorac Surg. 2013;2(6):683-692.

23. Mauri L, Foster E, Glower DD et al. 4-Year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. J Am Coll Cardiol. 2013;62(4):317-328.

24. Gammie JS, Sheng S, Griffith BP et al. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg. 2009;87(5):1431-1437.

Figure Legends

Figure 1. Flow diagram showing patient selection.

Figure 2. Kaplan Meier curves showing survival rates for the two groups in the unmatched analysis (A) and in the propensity score matched analysis (B).

Figure 3. MV Repair rates overtime.

Table 1. Preoperative characteristics before and after propensity score matching

	Unmatched Analysis				Matched Analysis			
	DMV only	DMV+CABG	SMD	p- value	DMV only	DMV+CABG	SMD	p-value
	559	186			134	134		
Age, years (median (IQR))	69.8 (61-75.9)	70.2 (64-76.1)	0.162	0.07	71.5 (65-77.8)	69.9 (64.2- 76)	0.09	0.99
Female gender (%)	185 (33.1)	36 (19.4)	0.316	<0.01	27 (20.1)	27(20.1)	<0.01	1
NYHA class > 3 (%)	272 (48.7)	91 (48.9)	0.005	1	66 (49.3)	62 (46.3)	0.06	0.68
CCS Class > 3 (%)	9 (1.6)	32 (17.2)	0.554	<0.01	8 (6)	12 (9)	0.11	0.45
Diabetes (%)	25 (4.5)	19 (10.2)	0.222	<0.01	8 (6)	10 (7.5)	0.06	0.80
Hypertension (%)	242 (43.3)	107 (57.5)	0.288	<0.01	72 (53.7)	70 (52.2)	0.03	0.89
Active Smoker (%)	21 (3.8)	8 (4.3)	0.028	0.91	7 (5.2)	4 (3)	0.10	0.43
COPD (%)	55 (9.8)	18 (9.7)	0.005	1	17 (12.7)	13 (9.7)	0.09	0.56
Previous CVA (%)	34 (6.1)	19 (10.2)	0.151	0.09	11 (8.2)	15 (11.2)	0.10	0.50
PVD (%)	20 (3.6)	17 (9.1)	0.229	<0.01	7 (5.2)	6 (4.5)	0.03	1
Logistic Euroscore (median(IQR))	5 (3-7)	6 (5-8)	0.466	<0.01	6 (5-8)	6(5-8)	0.07	0.24
Urgent surgery (%)	87 (15.6)	67 (36.0)	2.891	<0.01	31 (23.1)	35 (26.1)	0.07	0.64
Redo-surgery	54(9.7)	7(3.8)	0.237	<0.01	8(6)	7(5.2)	0.03	1
Previous MI (%)	24 (4.3)	48 (25.8)	0.631	<0.01	15 (11.2)	19 (14.2)	0.09	0.54
Previous PCI (%)	11 (2.0)	12 (6.5)	0.225	<0.01	9(6.7)	5(3.7)	0.13	0.42
MV Replacement (%)	164 (29.3)	69 (37.1)	0.165	0.06	43 (32.1)	54 (40.3)	0.17	0.25
Reduced LVEF (%)	113 (20.2)	80 (43.0)	0.506	<0.01	45 (33.6)	47 (35.1)	0.03	0.87
Number of CABG								
0 grafts	559(100)	0(0)			134(100)	0(0)		

1 graft	0(0)	78(41.9)	0(0)	69(51.5)
2 grafts	0(0)	63(21.5)	0(0)	41(30.6)
3 grafts	0(0)	37(19.9)	0(0)	20(14.9)
4 grafts	0(0)	8(4.3)	0(0)	4(3)

Definitions: NYHA: New York Heart Association, CCS: Canadian Cardiovascular Surgery, COPD: Chronic Obstructive Pulmonary Disease, CVA: cerebro-vascular accident, PVD: peripheral vascular disease, MI: myocardial infarction, PCI: Percutaneous Coronary Intervention, MV: mitral valve, LVEF: left ventricular Ejection Fraction, SMD: Standardized mean difference

Table 2. Post-operative Outcomes before and after matching

	Unmatched Analysis†			Matched Analysis‡		
	DMV only	DMV+CABG	p-value	DMV only	DMV + CABG	p-value
	559	186		134	134	
CPB Time, min (median(IQR))	112 (91.5-135)	128 (110-160)	<0.01	114(89-131.8)	127 (110-155)	0.02
CA Time, min (median(IQR))	80 (65-98)	84.5 (73.25-102)	0.01	80 (64-98)	85 (74-98.8)	0.16
In Hospital Mortality	21 (3.8)	11 (5.9)	0.29	6 (4.5)	9 (6.7)	0.44
Post-operative CVA	7 (1.3)	0 (0.0)	0.27	3 (2.2)	0 (0.0)	0.09
Post-operative dialysis	5 (0.9)	3 (1.6)	0.68	3 (2.2)	2 (1.5)	0.65
Re-sternotomy for bleeding	25(4.5)	13(6.9)	0.24	6(4.5)	7(5.2)	0.76
Use of IABP	0(0)	0(0)	NA	0(0)	0(0)	NA
Composite outcome	30(5.4)	12(6.5)	0.71	11(8.2)	10(7.5)	0.82
Length of hospital Stay, days (median (IQR))	8(6-11)	9.5 (7-14)	<0.01	9(7-12.8)	9 (7-13.8)	0.35

Definitions: CPB: Cardio-Pulmonary Bypass time, CA: Cardioplegic Arrest, CVA: cerebrovascular accidents, IABP: intra-aortic balloon pump.

†: Unpaired Mann-Whitney test for numerical variables, Chi-squared or Fisher-exact test for categorical variables

‡: Paired Mann-Whitney test for numerical variables, McNemar's test for categorical variables

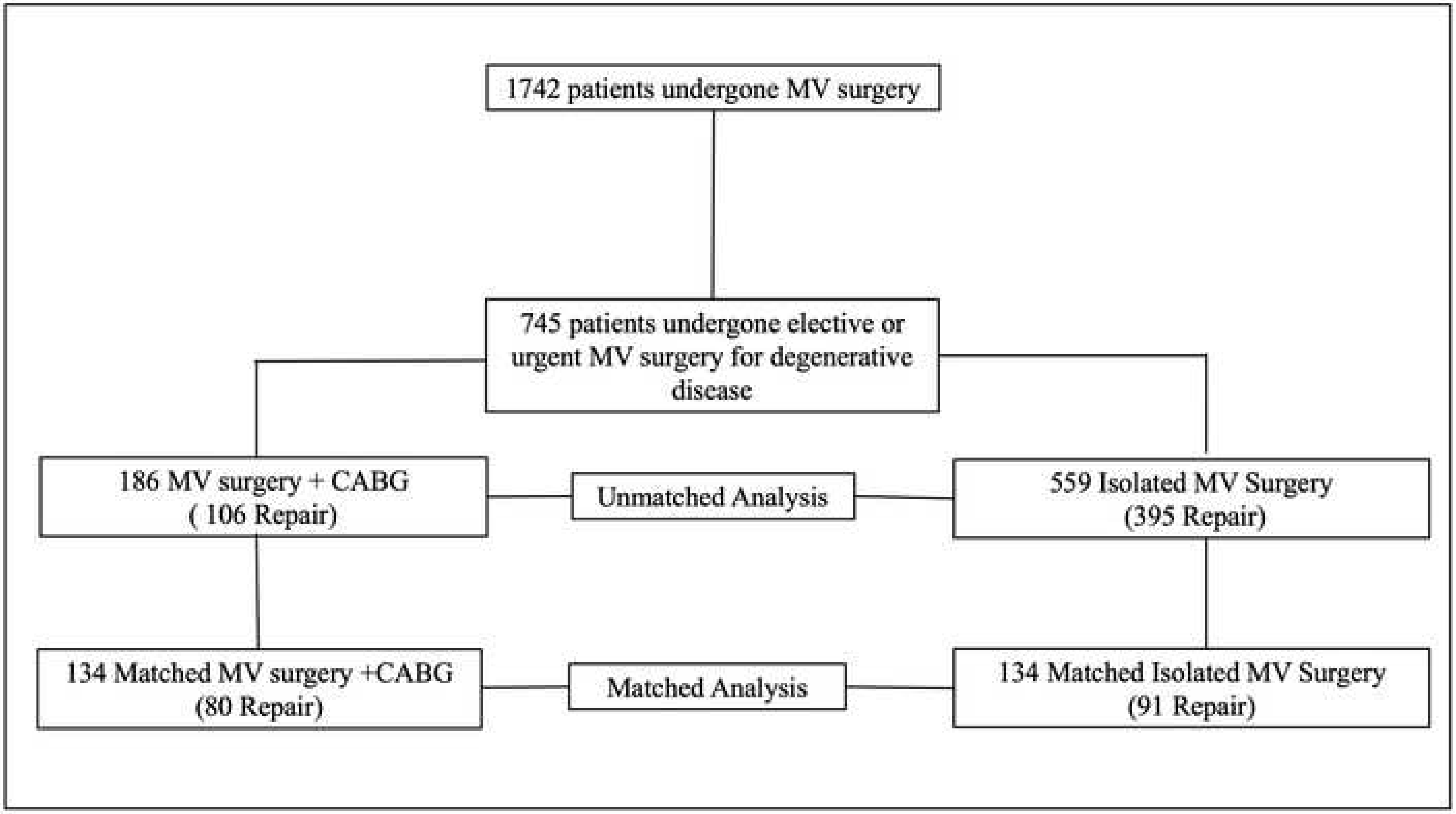
Table 3. Post-operative Outcomes in progressive surgical periods

	1st Period (2000-2004)	2nd Period (2005-2009)	3rd Period (2009-2014)	p value
	85	118	374	
MV Repair	20(23.5%)	118(65.9%)	374(77.8%)	<0.01
In Hospital Mortality	6(7.1%)	5(2.8%)	21(4.4%)	0.277
Post-operative CVA	2(2.4%)	4(2.2%)	1(0.2%)	0.02
Post-operative dialysis	2(2.4%)	4(2.2%)	2(0.4%)	0.06
Composite outcome	8(9.4%)	12(6.7%)	22(4.6%)	0.159
Length of hospital Stay, days (median (IQR))	9(7-11)	9(6-12)	8(6-12)	0.676

Definitions: MV: Mitral Valve; CVA: cerebrovascular accident; IQR: interquartile range.

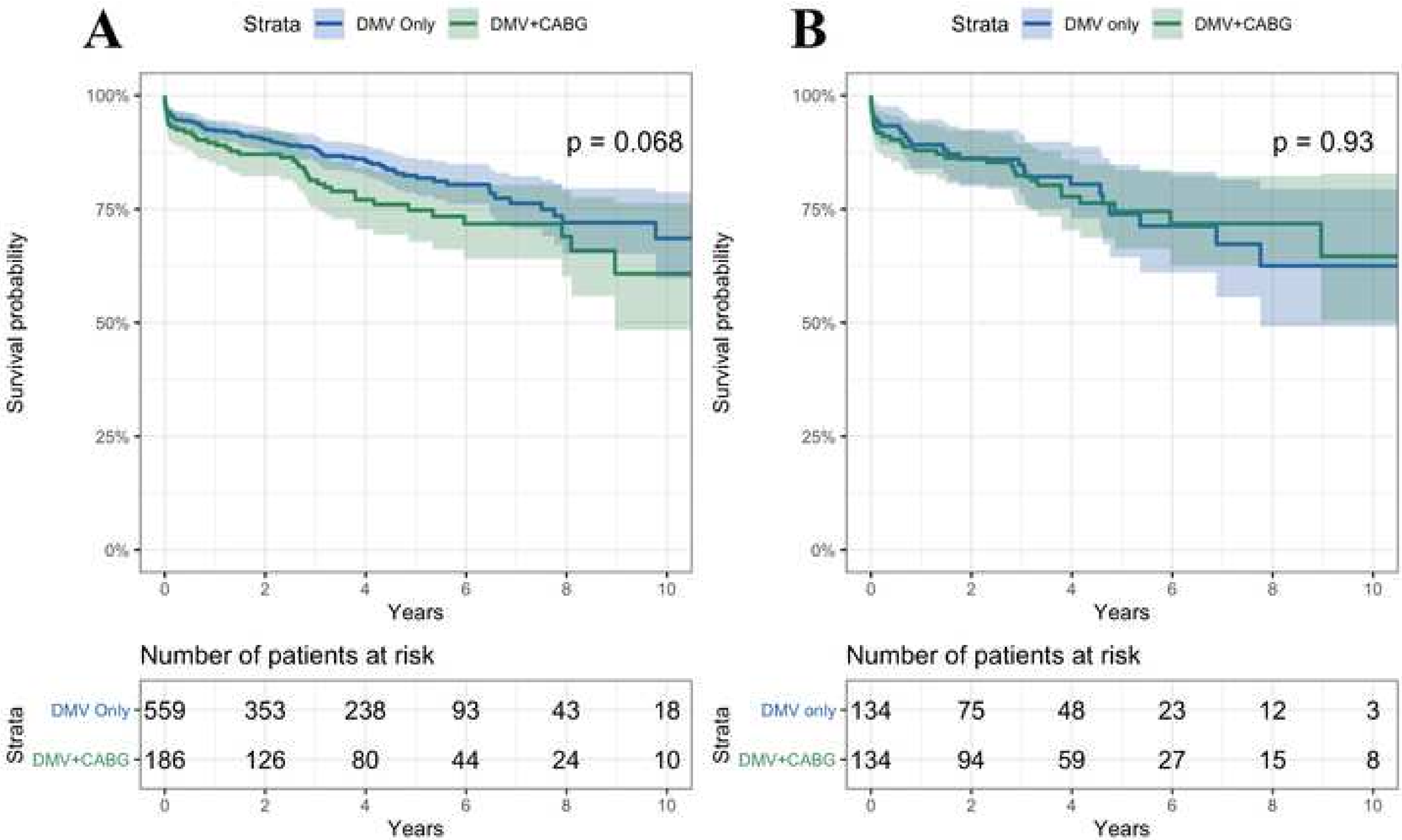
FINAL-FIG1

Click here to access/download;Figure;19-02058-fig1.tif



FINAL-FIG2

Click here to access/download;Figure;19-02058-fig2.tif



FINAL-FIG3

Click here to access/download;Figure;19-02058-fig3.tif

Combined degenerative mitral valve and coronary surgery: early outcomes and 10-year survival

Short title: Degenerative mitral and coronary surgery

Vito D. Bruno[1], PhD Mustafa Zakkar[1], PhD Gustavo Guida[1], MD Filippo Rapetto[1], MD Asif Rathore[1], FRCS and Raimondo Ascione[1], FRCS

[1]Bristol Heart Institute, School of Clinical Sciences, University of Bristol, Bristol, UK

Corresponding author: Professor Raimondo Ascione
Chair of Cardiac Surgery & Translational Research
Faculty of Health Science
University of Bristol
Marlborough Street,
BS2 8HW, Bristol, UK
Telephone Number: +44 01173423286
Email R.Ascione@bristol.ac.uk

Total Word count: 4667~~4465~~

Key words: mitral regurgitation, degenerative mitral valve surgery, coronary surgery, survival.

Abstract

Background: To investigate the impact of combined degenerative mitral valve (DMV) and coronary artery bypass grafting ~~(CABG)~~ surgery (CABG+DMV) versus DMV surgery only on in-hospital health outcome and 10-year survival.

Methods: 745 patients with DMV disease were identified. Of these, 186 (24.9%) were affected also by coronary disease receiving combined DMV+CABG. They were compared with the remaining 559 patients receiving DMV only surgery in terms of in-hospital, 1, 5, and 10-year survival. We evaluated a short-term composite outcome of hospital mortality, acute kidney ~~injury, cerebro~~injury, cerebro-vascular events and ~~severe~~ low cardiac output requiring postoperative use of intra-aortic balloon pump. In addition, we assessed mitral valve ~~MV~~ repair rates over time and their correlation with long-term survival. To minimise bias, we conducted a propensity score matching.

Results: DMV+CABG surgery was associated with a similar incidence of composite endpoint compared to DMV surgery alone (6.5 vs 5.4 %, p=0.71 in the unmatched analysis and 7.5% vs 8.2%, p=0.82 in the matched analysis). 10-year survival was 70.5 vs 68.6 % (p=0.07) for the unmatched analysis and 64.6 vs 62.5 % (p=0.9) for the matched analysis, DMV+CABG vs DMV only respectively. Mitral valve~~MV~~ repair had a beneficial effect on short term outcomes and long-term mortality rates, regardless the presence of concomitant coronary surgery ~~CABG~~.

Conclusions: Combined DMV+CABG surgery is a very effective surgical treatment with high mitral valve ~~MV~~ repair rate. Early in-hospital outcome and long-term survival are comparable with ~~that of patients undergoing~~ DMV only surgery. In these combined procedures mitral valve~~MV~~ repair is associated with better long-term survival.

Abstract word count: 250~~46~~

List of abbreviations

AKI: Acute Kidney Injury

CABG: Coronary artery bypass grafting

CCS: Canadian Cardiovascular Society

CPB: Cardio-Pulmonary Bypass

CT: Computed Tomography

CVA: Cerebro Vascular Accidents

DMV: Degenerative Mitral Valve

DMV+ CABG: Degenerative mitral valve associated to coronary artery bypass grafting

HR: Hazard Ratio

IABP: Intra-Aortic Balloon Pump

IMV: Ischaemic Mitral Valve

IQR: Inter-quartile Range

LCO: Low Cardiac Output

LVEF: Left Ventricular Ejection Fraction

MI: Myocardial Infarction

MR: Mitral Regurgitation

MV: Mitral Valve

NHS: National Health Service

NYHA: New York Heart Association

OR: Odds Ratio

PCI: Percutaneous Coronary Intervention

SMD: Standardised Mean Difference

UK: United Kingdom

US: United States

Introduction

Combined coronary artery bypass grafting (CABG) and valve surgery is generally considered a predictor of mortality, complications and reduced long-term survival [1]. Data from the UK and USA registries suggest that combined mitral valve (MV) and coronary surgery is associated with a 3 to 5 folds increase of post-operative mortality compared to isolated MV procedures [1,2]. The UK registry suggests that in 2015 the 30-day mortality rate for combined MV and coronary surgery was 5.16% versus 2.83% for isolated MV surgery [2] and a recent report from >1200 US MEDICARE Hospitals suggests that combined MV and CABG surgery is associated with hospital mortality of >10% and reduced long-term survival rates [1]. However, this report generalises across the whole MV surgery spectrum, with no distinction across the different types of MV disease. Patients with ischemic mitral valve (IMV) disease undergoing combined IMV+CABG surgery are genuinely at high risk of in-hospital mortality and reduced long-term survival [3]. Conversely, surgery for isolated degenerative mitral valve (DMV) disease is associated with lower mortality rate and superior long-term survival rates, especially when reparative techniques are used in high-volume centres [1,4,5]. Only few studies have investigated the impact of combined DMV and CABG surgery (DMV+CABG) on health outcomes [6]. Hence, outcome data associated with combined DMV+CABG are either still missing or poorly understood. Key examples of missing data include actual rates of in-hospital mortality and complications, long-term survival, reliability of logistic Euroscore in predicting mortality and impact of combined DMV+CABG on MV repair rates [7]. The aim of this study was to investigate the impact of the specific combination of degenerative mitral valve plus coronary (DMV+CABG) surgery versus DMV alone on 30-day mortality, hospital complication rates, MV repair rates, and on 1, 5, and 10-year survival and reoperation rates. In addition, we evaluated the impact of the MV repair on the risk of early and long-term mortality in combined procedures compared to isolated DMV.

Patients and Methods

The key rationale for designing this study was to test the null hypothesis that CABG would not increase operative risks when specifically combined with degenerative MV disease. To this end we elected to undertake a retrospective analysis of prospectively collected data derived from our internal database validated and stored by an independent team, as part of the UK National Registry for Cardiac Surgery. The study protocol followed the local Institutional Clinical Audit Review Board and patient consent was waived.

Patient selection

Patient selection is shown in **Figure 1**. From January 2000 to March 2015 a total of 1,742 patients underwent any procedures involving mitral valve surgery at our institution (for more details see **Supplemental table 1 and 2 and Supplemental file** Patient Selection). A propensity matched analysis was conducted to minimize the impact of preoperative differences: after matching, 134 patients for each group were compared.

Data collection and clinical management

Baseline data included clinical characteristics, symptom status and past medical history of the patients. Logistic Euroscore was calculated according to established method [8]. Diagnosis of severe DMV and coronary disease was based on clinical history, preoperative echocardiograms and baseline coronary angiography. Elective patients were defined as those admitted from home, whereas urgent patients were those admitted from another hospital and requiring surgery within 7-10 day before discharge. Left ventricular ejection fraction (LVEF) was derived from baseline echocardiogram and classified as reduced if less than 50%. The surgical technique and postoperative care used was in keeping with surgeon's preference (for more details see **Supplemental file** – Surgical Technique and Outcomes). Intraoperative and postoperative data collection and clinical management was as previously reported [9,10]. Late survival data after discharge were obtained from the UK National Health Service (NHS) tracing service with the latest data obtained in June 2015.

Outcome Measures and definitions

We used a composite outcome of in-hospital mortality, acute kidney injury (AKI), cerebro-vascular accidents (CVA) and severe low cardiac output (LCO). We also collected generic in-hospital outcome including reopening for bleeding, duration of hospital stays,1, 5 and 10-year survival as well as 5- and 10-years MV reoperation rates. In-hospital mortality was defined as a death by any cause occurred at any time before discharge regardless the length of hospital stays. CVA consisted of any new post-operative stroke identified clinically and/or by Computed Tomography (CT) scan. Occurrence of acute kidney injury was defined as need for postoperative hemofiltration/dialysis. Severe LCO was defined as the need to insert intra-operatively or postoperatively an intra-aortic balloon pump (IABP). Overtime, the rate of MV repair in both groups was assessed across consecutive 5-yer time periods.

Statistical analysis

Data are presented as mean ± one standard deviation for numerical variables that were normally distributed and as median and interquartile range (IQR) for the numerical variables not normally distributed. Categorical variables are shown as count and percentages. Comparison between numerical variables has been conducted using unpaired Student t-test if normally distributed and Mann-Whitney U test if not normally distributed. Categorical variables have been compared using Pearson Chi-square test or Fisher exact test as appropriate. A multiple logistic regression model has been used to identify predictors of in-hospital mortality: the final model was obtained with a stepwise approach. Survival analysis was conducted comparing the survival functions of the two groups using Log-Rank test and Kaplan Meier Curves. In addition, a propensity score matching analysis was conducted to account for differences in baseline characteristics between groups. The matching process included the following variables: gender, New York Heart Association (NYHA) class, Canadian Cardiovascular Society (CCS) class, diabetes, hypertension, smoking history, peripheral vascular disease, logistic Euroscore, use of baseline inotropes, previous percutaneous coronary intervention (PCI), previous myocardial infarction (MI), reduced LVEF (<50%), nonelective surgery and re-operation. The nearest neighbour method was used, and the balance checked with standardised mean differences (SMD). After propensity score matching, variables were compared using paired Student t-test or paired Wilcoxon test for continuous variables and McNemar (for dichotomous variables) and Chi-square test for ordinal categorical variables and a conditional logistic regression model accounting for matching index was developed to evaluate the predictors of the in-hospital mortality. Patients were also divided by time-period of observation to allow a descriptive sub-analysis of changes in MV repair rate and key early health outcome overtime. All tests were two-sided with the alpha level set at 0.05 for statistical significance.

Missing values were addressed with simple imputation methods. The statistical analysis was computed using R version 3.0.2 (R Core Team. R Foundation for Statistical Computing, Vienna, Austria).

Results

Preoperative characteristics of the patients before and after propensity score matching are shown in **Table 1.**

Unmatched analysis

The mean age of the overall population was 67.6 ± 11.8 years and logistic Euroscore was significantly higher in the DMV+CABG group (median 6 (IQR= 5-8) vs 5 (IQR = 3-7), $p < 0.01$).

Intra-operative characteristics and post-operative outcomes of unmatched analysis are shown in **Table 2**. As expected, cardiopulmonary bypass (CPB) time and aortic cross clamp times were longer in the DMV+CABG group. The predefined composite outcome did not differ between groups (6.5 % vs 5.4%, p=0.71). In-hospital mortality rate was 5.9% vs 3.8% (p = 0.29); CVA was 0% vs 1.3 % (p=0.27); AKI was 1.6% vs 0.9% (p = 0.68), while the occurrence of LCO was 0.0% in both groups, all DMV+CABG group vs DMV only group respectively. Reopening for bleeding was 6.9% vs 4.5% (p=0.71). Length of hospital stay was longer in this DMV+CABG vs DMV only group (median 9.5 vs 8 days (p = 0.04). The univariable logistic regression model did not identify DMV+CABG as an independent predictor of the composite (OR 1.61, 95% CI 0.73-3.34, p = 0.21) or of in-hospital mortality (OR 1.61, 95% CI 0.73-3.34, p = 0.21). The adjusted multiple logistic regression model confirmed that DMV+CABG is neither a predictor of the predefined composite endpoint nor of in-hospital mortality. This model identified 3 predictors of in-hospital mortality including the use of MV replacement (OR 2.52, 95% CI 1.14-5.73, p =0.02), logistic Euroscore (OR 1.40, 95% CI 1.23 – 1.50, $p < 0.01$), and prolonged CPB time (OR 1.01, 95% CI 1.002-1.02, p = 0.01). Long term survival rates for the unmatched analysis were similar between the two groups (**Figure 2-A**): DMV+ CABG patients had a survival rate of 94.4%

at 1 year, 77.5% at 5-year and 63% at 10 years vs 93.2% at 1 year, 85.3% at 5 years and 70.6% at 10 years for the DMV only group (p = 0.18). DMV+CABG did not affect the survival rates when assessed by a Cox proportional Hazard model (HR 1.58, 95% CI 0.87-2.04, p = 0.18).

Matched analysis

After propensity score matching (**Table 1**) the surgical operative times were found to be longer in the DMV+CABG with a median CPB time of 127 minutes vs 114 minutes in the DMV only group (p = 0.02) and a median aortic cross-clamp time of 85 vs 80 minutes respectively (p = 0.16). The MV repair rates were 59.7% vs 68.9%, p=0.2. in the DMV+CABG vs DMV alone groups respectively. The predefined composite outcome did not differ between groups (7.5 % vs 8.2%, p=0.82). In-hospital mortality was 6.7% in the DMV+CABG vs 4.5% for the DMV only group (p=0.44), while post-operative CVA was 0% vs 2.2 (p = 0.65), post-operative dialysis was 1.5 vs 2.2% (p = 0.65), and LCO was 0.0% in both groups, respectively. Length of hospital stay was also similar between the groups: median 9 (IQR 7-12.8) vs median 9(IQR 7-13.8) respectively (p = 0.35). The survival rates were 88 % at 1 year, 74.5 % at 5 years and 64.6% at 10 years for the DMV+CABG group and 89.2% at 1 year, 73.9% at 5 years and 62.5% at 10 years for the DMV only group(p=0.9) (**Figure 2-B**). No independent predictors of mortality were found.

Rates of mitral valve repair overtime and impact on short- and long-term outcome

The overall MV repair rates were 62.9% vs 70.7%, (p=0.06) in the DMV+CABG vs DMV alone groups respectively. Differences in MV repair and health outcome by time-period are shown in **Table 3 and Figure 3**. The period between year 2000 and 2004 was characterised by a low rate of MV repair in our centre. However, this increased significantly after year 2004 with a peak of MV repair rate of 88.5% in 2009 (**Figure 3**). The main health outcomes at different time periods is shown in **Table 3**: mortality rate was lower in the period between 2005-2009, while the lowest rate of composite health outcome was found in the final part of the series in concomitance with the highest repair rate. Higher rates of MV repair were also associated with higher long-term survival with an HR of 0.46 (95% CI 0.35-0.66).

When adjusted for combined procedure (CABG) and cross-clamp time the beneficial effect of the MV repair on long-term survival was still confirmed (HR 0.47, 95% CI 0.33-0.68), showing that the complexity and the length of the surgery has no impact on the intrinsic beneficial effect of the repair procedure. During the follow up time, fifteen patients (2.01%) underwent a reoperation. Of these, 12 procedures (1.63%) consisted of re-operations involving the mitral valve including 10 isolated MV reoperations and 2 procedures combined with aortic valve replacement. Of note, freedom from MV reoperation at 10 years was 97.2% for the DMV+CABG group and 97.9% for the DMV only group(p=0.61).

Comment

The combination of CABG and valve procedures has been generally associated with worst outcome after cardiac surgery [1,11-13]. Combined MV and CABG surgery has been largely investigated in the context of ischaemic mitral valve disease [14,15] with the results of this MV specific disease often uncritically generalised across the non-ischemic mitral disease spectrum[1], affecting the informed consenting of patients and the decision-making process toward percutaneous and/or medical treatment alternatives [16-18]. Yet, little is known on the outcome of DMV+CABG surgery [6,19].

Our study shows that combined DMV+CABG has a similar rate of mortality, hospital complications, MV repairs, and long-term survival compared to DMV surgery alone. These findings highlight that patients afflicted by combined severe DMV and coronary disease should be offered combined DMV+CABG surgery instead of alternative and less validated alternatives.

In this study, DMV+CABG surgery was not associated with worse outcome compared with DMV surgery alone for any of the health outcome measured. The only consistent difference observed was the longer CPB time in the combined group. Even in the unmatched analysis all the outcome measures evaluated showed similar results compared to DMV only group.

~~Contrary to~~ A~~a~~ recent large report from US [1] found CABG to be an independent predictor of both short and long-term mortality, while this was not the case in our study. ~~, our study did not show the~~

~~DMV+CABG surgery to be a predictor of in-hospital and long-term mortality; our early and late mortality rates were lower than those described in the US report.~~ However, the study population of the US report [1] was on average 5 years older compared to our patient cohort and encompassed a variety of valve pathologies and surgical procedures. Hence, a comparative evaluation is not appropriate as the observed results could reflect differences in baseline risk profile, surgical and anaesthetic practice as well as a different period of observation. In addition, observed outcome in the two studies might also reflect differences in volume of MV surgery and MV repair rates between centres [1]. In this study the rates of MV repair was 68.7% with no differences between groups, despite is an historical series, with 25% of patients receiving non-isolated MV, 8.2% having redo surgery, median age being 70 years, and 25% of patients being urgent admissions. As expected, the rate of MV repair rose over time reaching 85-90% by 2008. Of note, MV repair was associated with better short-term outcome and long-term survival.

Previous studies have suggested that Euroscore may underestimate the mortality risk for combined surgery: in a study published in 2004, Karthik and colleagues reported a mortality rate after CABG plus valve surgery of 8.7% compared to a predicted value (additive Euroscore) of 6.7% [20]. Similar results were reported in another study suggesting that the Euroscore underestimated the impact of combined procedures (O/E = 1.09, p < 0.001) [21].

The findings of this study confirm that combined DMV+CABG surgery is associated with low in-hospital risk and excellent long-term survival particularly when MV repair is used. This confirms that a surgical practice by MV repair expertise may improve patient benefit and use of hospital resources. In addition, these findings may help the decision-making process toward surgery, instead of less validated percutaneous techniques or medical treatment alone. Recent evidence from meta-analysis and randomised trial suggest that the mitral clip procedure is associated with a very high rate of on table residual 2+ m~~M~~itral regurgitation (MR), 7.3% of mortality at 1 year, and a freedom from combined death, repeat surgery, or grade 3+ or 4+ recurrent MR of only 39.8% at 4 years. These reports also highlight a need for open reoperation rates at 4 year of 25% in patients undergoing primary mitral clip treatment [22,23]. This study also suggests that patients needing combined DMV+CABG should not be regarded at high risk. Instead they should be referred for conventional surgery to high-volume MV repair surgery centres for consideration.

The logistic regression model analysis did not identify DMV+CABG surgery as an independent predictor of mortality, while it confirmed that replacing the MV instead of repairing it is associated with worse health outcome. Others have already underlined this concept by showing that MV repair is the preferred option in these patients [7] with a reduced incidence of complications and mortality rate [24].

There are limitations to this study: it is a retrospective analysis and no data is presented on long-term cardiac related events including recurrence of MR and quality of life/symptoms. In addition, a relatively small number of patients was under observation at 10-year follow-up. However, our series with 100% follow-up survival data, low rate of early composite endpoint and very good long-term survival is still a valuable and real reflection of clinical efficacy and patient well-being. In addition, very few patients in the DMV only group (n=24) had mild or moderate coronary disease for which the Heart Team did not indicate the need for combined CABG surgery. Another possible limitation is related to the risk of Type II error and therefore the risk of non-rejection of a false null hypothesis as concomitant CABG is a recognised risk factor in valve surgery, hence larger studies are required to confirm our findings.

In conclusion this study suggests that combined DMV+CABG surgery is safe and effective with a 30-day mortality, complication rates, MV repair rates, and 1, 5, and 10-year survival comparable to DMV surgery only. It also indicates that MV repair should be the first choice in these combined cases of degenerative mitral valve and coronary disease due superior short-term health outcome and long-term survival beneficial effects. These findings, if confirmed by larger studies, have important clinical implications in terms of both referral pathways by surgical MV repair expertise and patient informing/consenting.

Acknowledgments

The authors would like to thank the clinical staff and the patients at the Bristol Heart Institute, University Hospital Bristol NHS Foundation Trust.

Funding statement

RA acknowledges support from the National Institute of Health Research Bristol Biomedical Research Centre, the British Heart Foundation [grants IG/14/2/30991, PG/10/40/28369, PG/16/104/32652], and Medical Research Council [grant MR/L012723/1].

Disclosures

The authors declare that they have no competing interests.

References

1. Vassileva CM, McNeely C, Spertus J, Markwell S, Hazelrigg S. Hospital volume, mitral repair rates, and mortality in mitral valve surgery in the elderly: An analysis of US hospitals treating Medicare fee-for-service patients. J Thorac Cardiovasc Surg. 2015;149(3):762-768.e1.

2. Bridgewater B, Keogh B, Kinsman R, Walton P. SCTS 6th National Adult Cardiac Surgical Database Report 2008.; 2008.

3. Wang L, Li B, Liu C, Rong T, Yu Y, Gu C. Short- and Medium-Term Effects of Combined Mitral Valve Surgery and Coronary Artery Bypass Grafting Versus Coronary Artery Bypass Grafting Alone for Patients with Moderate Ischemic Mitral Regurgitation: A Meta-Analysis. J Cardiothorac Vasc Anesth. 2016;30(6):1578-1586.

4. Coutinho GF, Antunes MJ. Mitral valve repair for degenerative mitral valve disease: surgical approach, patient selection and long-term outcomes. Heart. 2017;103(21):1663-1669.

5. Bridgewater B, Hooper T, Munsch C et al. Mitral repair best practice: proposed standards. Heart. 2006;92(7):939-944.

6. Dahlberg PS, Orszulak TA, Mullany CJ, Daly RC, Enriquez-Sarano M, Schaff H V. Late outcome of mitral valve surgery for patients with coronary artery disease. Ann Thorac Surg. 2003;76(5):1539-1548.

7. Javadikasgari H, Gillinov AM, Idrees JJ et al. Valve Repair Is Superior to Replacement in Most Patients With Coexisting Degenerative Mitral Valve and Coronary Artery Diseases. Ann Thorac Surg. 2016. 103(6):1833-1841.

8. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J. 2003;24(9):881-882.

9. Zakkar M, Bruno VD, Guida G, et al. Postoperative acute kidney injury defined by RIFLE criteria predicts early health outcome and long-term survival in patients undergoing redo coronary artery bypass graft surgery. J Thorac Cardiovasc Surg. 2016:152(1): 235-42.

10. Bruno VD, Zakkar M, Rapetto F et al. Early health outcome and 10-year survival in patients undergoing redo coronary surgery with or without cardiopulmonary bypass: a propensity score-matched analysis. Eur J Cardiothorac Surg. 2017;52(2):945-951.

11. Nicolini F, Agostinelli A, Fortuna D et al. Outcomes of patients undergoing concomitant mitral and aortic valve surgery: results from an Italian regional cardiac surgery registry. Interact Cardiovasc Thorac Surg. 2014;19(5):763-770.

12. Hannan EL, Racz MJ, Jones RH et al. Predictors of mortality for patients undergoing cardiac valve replacements in New York State. Ann Thorac Surg. 2000;70(4):1212-1218.

13. Leavitt BJ, Baribeau YR, DiScipio AW et al. Outcomes of patients undergoing concomitant aortic and mitral valve surgery in northern New England. Circulation. 2009;120(11 Suppl). S155-62.

14. Buja P, Tarantini G, Del Bianco F et al. Moderate-to-severe ischemic mitral regurgitation and multivessel coronary artery disease: Impact of different treatment on survival and rehospitalization. Int J Cardiol. 2006;111(1):26-33.

15. Fattouch K, Guccione F, Sampognaro R et al. POINT: Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. J Thorac Cardiovasc Surg. 2009;138(2):278-285.

16. Roques F, Nashef SA, Michel P et al. Risk factors and outcome in European cardiac surgery : analysis of the EuroSCORE multinational database of 19030 patients Risk factors and outcome in European cardiac surgery : analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15(6):816-822.

17. Shahian DM, He X, Jacobs J et al. The STS AVR+CABG Composite Score : A Report of the STS Quality Measurement Task Force. Ann Thorac Surg. 2014;97(5):1604-1609.

18. Hannan EL, Racz M, Culliford AT et al. Risk Score for Predicting In-Hospital / 30-Day Mortality for Patients Undergoing Valve and Valve/Coronary Artery Bypass Graft Surgery. Ann Thorac Surg. 2013;95(4):1282-1290.

19. Davarpasand T, Hosseinsabet A, Jalali A. Concomitant coronary artery bypass graft and aortic and mitral valve replacement for rheumatic heart disease : short-and mid-term outcomes. Interact Cardiovasc Thorac Surg 2015;21(May):322-328.

20. Karthik S, Srinivasan AK, Grayson AD et al. Limitations of additive EuroSCORE for measuring risk stratified mortality in combined coronary and valve surgery. Eur J Cardiothorac Surg 2004;26(2):318-322.

21. Atik FA, Cunha CR. Impact of type of procedure and surgeon on EuroSCORE operative risk validation. Rev Bras Cir Cardiovasc 2014;29(2):131-139.

22. Wan B, Rahnavardi M, Tian DH et al. A meta-analysis of MitraClip system versus surgery for treatment of severe mitral regurgitation. Ann Cardiothorac Surg. 2013;2(6):683-692.

23. Mauri L, Foster E, Glower DD et al. 4-Year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. J Am Coll Cardiol. 2013;62(4):317-328.

24. Gammie JS, Sheng S, Griffith BP et al. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg. 2009;87(5):1431-1437.

Figure Legends

Figure 1. Flow diagram showing patient selection.

Figure 2. Kaplan Meier curves showing survival rates for the two groups in the unmatched analysis (A) and in the propensity score matched analysis (B).

Figure 3. MV Repair rates overtime.

Table 1. Preoperative characteristics before and after propensity score matching

	Unmatched Analysis				Matched Analysis			
	DMV only	DMV+CABG	SMD	p- value	DMV only	DMV+CABG	SMD	p-value
	559	186			134	134		
Age, years (median (IQR))	69.8 (61-75.9)	70.2 (64-76.1)	0.162	0.07	71.5 (65-77.8)	69.9 (64.2- 76)	0.09	0.99
Female gender (%)	185 (33.1)	36 (19.4)	0.316	<0.01	27 (20.1)	27(20.1)	<0.01	1
NYHA class > 3 (%)	272 (48.7)	91 (48.9)	0.005	1	66 (49.3)	62 (46.3)	0.06	0.68
CCS Class > 3 (%)	9 (1.6)	32 (17.2)	0.554	<0.01	8 (6)	12 (9)	0.11	0.45
Diabetes (%)	25 (4.5)	19 (10.2)	0.222	<0.01	8 (6)	10 (7.5)	0.06	0.80
Hypertension (%)	242 (43.3)	107 (57.5)	0.288	<0.01	72 (53.7)	70 (52.2)	0.03	0.89
Active Smoker (%)	21 (3.8)	8 (4.3)	0.028	0.91	7 (5.2)	4 (3)	0.10	0.43
COPD (%)	55 (9.8)	18 (9.7)	0.005	1	17 (12.7)	13 (9.7)	0.09	0.56
Previous CVA (%)	34 (6.1)	19 (10.2)	0.151	0.09	11 (8.2)	15 (11.2)	0.10	0.50
PVD (%)	20 (3.6)	17 (9.1)	0.229	<0.01	7 (5.2)	6 (4.5)	0.03	1
Logistic Euroscore (median(IQR))	5 (3-7)	6 (5-8)	0.466	<0.01	6 (5-8)	6(5-8)	0.07	0.24
Urgent surgery (%)	87 (15.6)	67 (36.0)	2.891	<0.01	31 (23.1)	35 (26.1)	0.07	0.64
Redo-surgery	54(9.7)	7(3.8)	0.237	<0.01	8(6)	7(5.2)	0.03	1
Previous MI (%)	24 (4.3)	48 (25.8)	0.631	<0.01	15 (11.2)	19 (14.2)	0.09	0.54
Previous PCI (%)	11 (2.0)	12 (6.5)	0.225	<0.01	9(6.7)	5(3.7)	0.13	0.42
MV Replacement (%)	164 (29.3)	69 (37.1)	0.165	0.06	43 (32.1)	54 (40.3)	0.17	0.25
Reduced LVEF (%)	113 (20.2)	80 (43.0)	0.506	<0.01	45 (33.6)	47 (35.1)	0.03	0.87
Number of CABG								
0 grafts	559(100)	0(0)			134(100)	0(0)		

1 graft	0(0)	78(41.9)	0(0)	69(51.5)
2 grafts	0(0)	63(21.5)	0(0)	41(30.6)
3 grafts	0(0)	37(19.9)	0(0)	20(14.9)
4 grafts	0(0)	8(4.3)	0(0)	4(3)

Definitions: NYHA: New York Heart Association, CCS: Canadian Cardiovascular Surgery, COPD: Chronic Obstructive Pulmonary Disease, CVA: cerebro-vascular accident, PVD: peripheral vascular disease, MI: myocardial infarction, PCI: Percutaneous Coronary Intervention, MV: mitral valve, LVEF: left ventricular Ejection Fraction, SMD: Standardized mean difference

Table 2. Post-operative Outcomes before and after matching

	Unmatched Analysis†			Matched Analysis‡		
	DMV only	DMV+CABG	p-value	DMV only	DMV + CABG	p-value
	559	186		134	134	
CPB Time, min (median(IQR))	112 (91.5-135)	128 (110-160)	<0.01	114(89-131.8)	127 (110-155)	0.02
CA Time, min (median(IQR))	80 (65-98)	84.5 (73.25-102)	0.01	80 (64-98)	85 (74-98.8)	0.16
In Hospital Mortality	21 (3.8)	11 (5.9)	0.29	6 (4.5)	9 (6.7)	0.44
Post-operative CVA	7 (1.3)	0 (0.0)	0.27	3 (2.2)	0 (0.0)	0.09
Post-operative dialysis	5 (0.9)	3 (1.6)	0.68	3 (2.2)	2 (1.5)	0.65
Re-sternotomy for bleeding	25(4.5)	13(6.9)	0.24	6(4.5)	7(5.2)	0.76
Use of IABP	0(0)	0(0)	NA	0(0)	0(0)	NA
Composite outcome	30(5.4)	12(6.5)	0.71	11(8.2)	10(7.5)	0.82
Length of hospital Stay, days (median (IQR))	8(6-11)	9.5 (7-14)	<0.01	9(7-12.8)	9 (7-13.8)	0.35

Definitions: CPB: Cardio-Pulmonary Bypass time, CA: Cardioplegic Arrest, CVA: cerebrovascular accidents, IABP: intra-aortic balloon pump.

†: Unpaired Mann-Whitney test for numerical variables, Chi-squared or Fisher-exact test for categorical variables

‡: Paired Mann-Whitney test for numerical variables, McNemar's test for categorical variables

Table 3. Post-operative Outcomes in progressive surgical periods

	1st Period (2000-2004)	2nd Period (2005-2009)	3rd Period (2009-2014)	p value
	85	118	374	
MV Repair	20(23.5%)	118(65.9%)	374(77.8%)	<0.01
In Hospital Mortality	6(7.1%)	5(2.8%)	21(4.4%)	0.277
Post-operative CVA	2(2.4%)	4(2.2%)	1(0.2%)	0.02
Post-operative dialysis	2(2.4%)	4(2.2%)	2(0.4%)	0.06
Composite outcome	8(9.4%)	12(6.7%)	22(4.6%)	0.159
Length of hospital Stay, days (median (IQR))	9(7-11)	9(6-12)	8(6-12)	0.676

Definitions: MV: Mitral Valve; CVA: cerebrovascular accident; IQR: interquartile range.